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Atherogenesis 2002

New Concepts In Plaque Vulnerability and C Reactive Protein

Marla J. De Jong, RN, MS, CCNS, CCRN, CEN, Major

Objectives

- Discuss history of traditional thoughts on atherogenesis and how they have changed
- Discuss basic science of atherogenesis
- Discuss concept of plaque vulnerability
- Discuss concept of inflammation and C-reactive protein and fibrinogen in atherogenesis

Atherogenesis – Past and Present

History of Atherogenesis

- Inevitable degenerative process
- Lipid storage disease
- Arteries viewed as inanimate tubes
- Plaque rupture
- Occlusive thrombus

Atherogenesis Today

- Inflammatory process
- Endothelial dysfunction
- Neurohormonal factors
- Vessel narrowing vs. dilation

Process of Atherogenesis

Arterial Anatomy

- Intimal layer
- Medial layer
- Adventitial layer

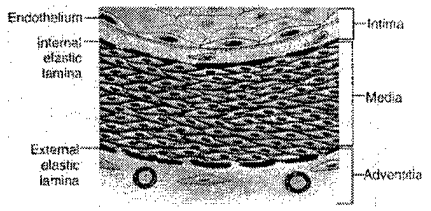


Figure: Cotran et al. 1999. Robbins Pathologic Basis of Disease, 6th ed., Saunders

Lesion Initiation

- Endothelial damage
- Adhesion and chemoattractant molecules
  - Inflammatory leukocytes recruited
  - Extracellular lipid accumulates
- Fatty streaks

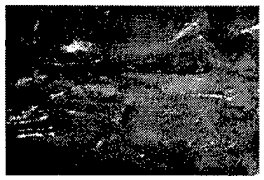


Figure: The Internet Pathology Laboratory for Medical Education

Fibrofatty stage

- Monocytes become macrophages
- Macrophages express scavenger receptors
- Macrophages ingest oxidized lipoproteins
- Lipid-laden foam cells arise

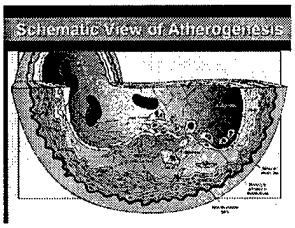


Figure: D. I. Simon TCTMD.com

Extracellular Lipid Pools

- Foam cell necrosis
- Small lipid pools
- Smooth muscle cell proliferation/migration
- Compensatory vessel wall dilation

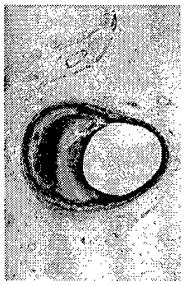
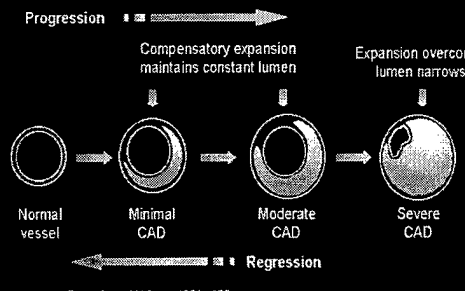


Figure: Vernava, AM; 2002. Circulation 105(8)

Glagov's Coronary Remodeling Concept



Core of Extracellular Lipid

- Lipid core forms
- Lesion expands
- Necrotic fatty core develops
- Fibrosis
- Effects of inflammatory mediators

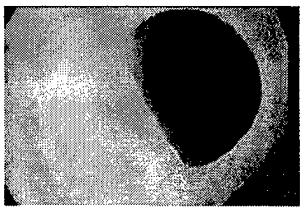


Figure: Davies, MJ. 1996. Circulation 94(8)

Lesion Progression

- Fibrous cap forms
- Lumen narrows
- Plaque may calcify

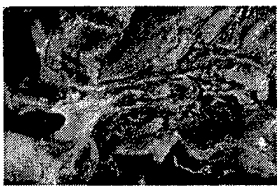


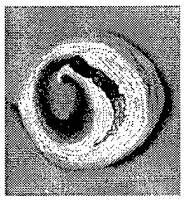
Figure: The Internet Pathology Laboratory for Medical Education

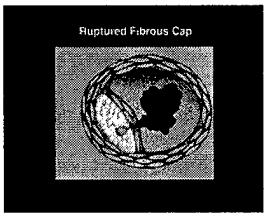
Metalloproteinases (MMPs)

- Source
- Actions
- Regulation

Fibrous Cap Rupture

- Coagulation factors contact lipid core
- Thrombosis on nonocclusive plaque





Figures by Mr. Henry Stiller

Figure by Mr. Henry Stiller

Endothelial Erosion

- Intimal erosion
- Blood & platelets exposed to subendothelial matrix
- Proteinases are expressed
- Mural thrombus

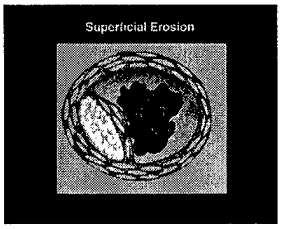


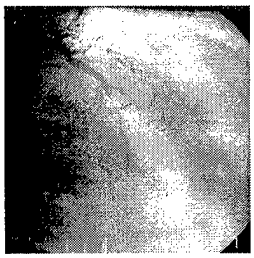
Figure by Mr. Henry Stiller

Plaque Healing

- Fibrinolysis
- Smooth muscle cell proliferation
- Increase in plaque size

Arteries at Risk

- Shape of arteries
- Areas with preexisting intimal thickening



Plaque Vulnerability

Plaque Vulnerability Defined

- Asymptomatic atherosclerotic lesions with a tendency to rupture
- High risk for luminal thrombosis

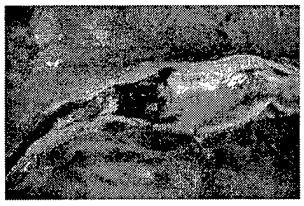


Figure: The Internet Pathology Laboratory for Medical Education

Characteristics of Stable Lesions

- Many smooth muscle cells
- Thick fibrotic caps
- Limited amount of lipid
- A small, noninflamed lipid core

Characteristics of Unstable Lesions

- Mechanical factors
  - Vasospasm
  - Turbulent blood flow
  - Large liquid lipid core
  - Plaque flexion
  - Thin fibrous cap

Liao, JK; 1998

Characteristics of Unstable Lesions

- Fibrous cap
  - Decreased collagen synthesis
  - Collagen degradation
  - Smooth muscle cell loss
  - Increased cytokines

Liao, JK; 1998

Characteristics of Unstable Lesions

- Plaque constituents
  - Increased esterified cholesterol
  - Decreased extracellular matrix
  - Increased metalloproteinases
  - Increased T cells and macrophages
  - Warmer plaque temperature

Liao, JK; 1998

Other Triggers of Plaque Disruption

- Circadian variation
- Seasonal variation
- Physical exertion
- Emotional stress

Doering, LV; 1999

Inflammation and Atherogenesis

Triggers for Inflammation

- Oxidized lipoproteins
- Dyslipidemia
- Hypertension
- Diabetes
- Obesity
- Infection

Libby, P et al., 2002

Consequences of Inflammation

- Endothelial inflammation
- Leukocyte recruitment & adhesion
- Local inflammatory response
- Atheroma thrombotic complications
- Acute coronary syndromes

Markers of Inflammation

C-Reactive Protein (CRP)

C-Reactive Protein

- Acute-phase marker
- Easily measured
- hs-CRP
- Levels > 2 µg/ml indicate high risk
- Significance

Functions of CRP

- Induces expression of adhesion molecules
- Mediates LDL update
- Induces monocyte recruitment into artery wall
- Enhances production of MCP-1

Research Related to CRP

- CARE Trial
- Physician's Health Study
- Women's Health Study
- PRINCE Trial
- AFCAPS/TexCAPS Study

Other Inflammatory Markers

Fibrinogen

- Major coagulation factor
- Acute phase reactant
- Increases during inflammation
- May promote smooth muscle cell growth
- May attract WBCs
- May promote platelet aggregation
- May inhibit fibrinolysis

Interleukin 6

- Cytokine
- Affects platelet production
- Induces synthesis of acute phase proteins
- Predictor for CAD
- Levels > 5 ng/L → increased mortality

Myeloperoxidase (MPO)

- A leukocyte enzyme
- Promotes oxidation of lipoproteins
- May activate latent MMPs
- May cause plaque destabilization
- May cause endothelial dysfunction
- Levels correlate with CAD

Cellular Adhesion Molecules

- Selectins
- B2 integrins
- Immunoglobins

B-Type Natriuretic Peptide

- Reflects neurohormonal activity
- Prognostic marker for ACS & CHF
- Increases with transient ischemia
- Threshold level 80 pg/mL

Pregnancy-Associated Plasma Protein A (PAPP-A)

- A potentially proatherosclerotic MMP
- Present in unstable plaques
- Levels > 10 mIU associated with ACS
- Higher in pts with USA/AMI than in controls

Diagnostic Tools for Inflammation

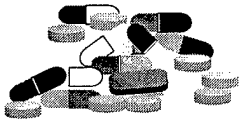
- Angioscopy
- Thermal imaging
- Lasers
- High resolution IVUS
- Light-tipped catheters
- MRI
- Raman spectroscopy
- Magnetic resonance coronary angiography
- Electron beam computed tomography
- PET scanning
- Optical coherence tomography
- Intravascular shear stress imaging
- Microbubble contrast echocardiographic imaging
- Many others

Is There Any Hope?

Risk Factors for Atherosclerosis

- Smoking
- Hypertension
- Hypercholesterolemia
- Infections
- Diabetes
- Hypoxia
- Oxidants
- Turbulent Flow

Risk Reduction



- Cholesterol reduction
- ACE inhibitors
- Clopidogrel
- Aspirin
- Glucose control
- Smoking cessation
- Exercise

Unanswered Questions

- Do measurements of inflammation identify pts at risk, and do these independently predict risk beyond currently used tools?
- Are specific therapies available to reduce serum levels of markers of inflammation?
- Do therapies that lower serum levels of inflammatory markers reduce CV risk?
- Which is the optimal test for prognostic evaluation?
- Which pt population should be targeted for testing?
- What is the role of endothelial dysfunction compared to other new risk assessment strategies?

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